REMARKS/ARGUMENTS

Claims 28-35 and 38-40 are pending in this application. The rejections to the presently pending claims are respectfully traversed.

I. Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 28-35 and 38-40 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility." (Page 2 of the instant Final Office Action). Claims 28-35 and 38-40 further remain rejected under 35 U.S.C. § 112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 28 of the instant Final Office Action).

Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the polypeptides of Claims 28-35 and 38-40 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without undue experimentation.

The gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the PRO1759 polypeptide.

Applicants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1759 polypeptide of SEQ ID NO:374. Using a PCR-based assay, Applicants made the assertion that the gene encoding for PRO1759 was significantly amplified (Example 143 of the instant specification). The Declaration by Dr. Audrey Goddard explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample, relative to a normal sample, is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Further, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. (See Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.* and Godbout *et al.* (of record). The gene amplification data, thus, is sufficient to confer patentable utility to the instantly claimed PRO1759 polypeptides.

The Examiner argues that "[n]ovel biological molecules lack well established utility and must undergo extensive experimentation." (Page 2 of the instant Final Office Action). In addition, the Examiner maintains that the present specification fails to disclose the physiological significance of the PRO1759 polypeptide or the correlation between PRO1759 DNA, PRO1759 mRNA and PRO1759 polypeptide expression as they relate colon and lung tumors. The Examiner continues to reject the instant polypeptide case asserting that "the skilled artisan would not know if the expression of the PRO1759 polypeptide would be upregulated, down-regulated, or unchanged in cancer." (Page 3 of the instant Final Office Action).

Applicants have disclosed that the PRO1759 gene is amplified in human colon and lung cancers. The present specification thus clearly discloses a particular biological activity: amplification in a particular type of cancer. Such amplification is useful, for example, in that the claimed PRO1759 polypeptides may be used as diagnostic markers for colon and lung cancer. Further, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. The articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, Bea *et al.* and Godbout *et al.*(of record), along with Declaration by Dr. Ashkenazi and Dr. Goddard, collectively teach that in general, gene amplification increases mRNA expression. With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted over one hundred references, along with the Declarations of Dr. Paul Polakis and Dr. Randy Scott (of record), which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

The Examiner has presented no evidence and no reasoning to suggest that these experimental results are in error. Thus, the specification, which discloses that PRO1759 is overexpressed in colon and lung tumors, demonstrates a biological activity related to the PRO1759 polypeptides that are bound by the claimed polypeptides. Accordingly, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1759 polypeptides.

The Examiner alleges that "the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue..." and assert that "it is not clear that the reported amplification is significant." (Pages 4-5 of the instant Final Office Action).

As discussed in Applicants' previous Responses, Applicants rely on the gene amplification data for patentable utility of the PRO1759 polypeptide. The gene amplification data for the gene encoding the PRO1759 polypeptide is clearly disclosed in the instant specification under Example 143. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO1759 in at least three of the tumors listed in Table 8. PRO1759 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$ fold amplification or 2.16 fold to 2.85-fold amplification in lung tumors HF000842 and HF001296, and in colon tumor center HF000795. (See Table 8 of the specification). Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO1759 polypeptide is significantly amplified in lung and colon tumors.

In addition, the previously submitted Declaration by Dr. Audrey Goddard clearly states:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Therefore, any gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay is considered useful as a marker for the diagnosis of cancer.

The Examiner further alleges, "One cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates." (Page 5 of the instant Final Office Action).

In response, Applicants refer to the previously submitted Declaration by Dr. Avi Ashkenazi, Ph.D. In particular, Dr. Ashkenazi is of the opinion that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker. As a result, the present gene amplification assay is a well-controlled experiment and gives rise to data of biological significance. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

The Examiner dismisses the Goddard declaration as "not pertinent" because it allegedly fails to address the issue of the claimed polypeptides. (Page 5 of the instant Final Office Action). The Examiner also contends that "the [Goddard] Declaration does not provide data such that the examiner can independently draw conclusions. Only Doctor Goddard's conclusions are provided in the declaration." (Page 6 of the instant Final Office Action).

Applicants point out that there is no requirement for a single declaration to show everything. Applicants have submitted Dr. Goddard's Declaration to show that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1759 is a diagnostic marker of colon and lung cancer. Applicants have submitted over a hundred references, along with the Declaration of Dr. Paul Polakis with their Preliminary Amendment filed on August 7, 2006, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants emphasize that the opinions expressed in the Goddard Declaration are all based on factual findings. Thus, Dr. Goddard explains that the TaqMan PCR assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. Further, Dr. Goddard explains that the assay is extremely

sensitive technique which leads to accurate determination of gene copy number. Dr. Goddard adds that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. For support, Dr. Goddard cites a number of references including a publication by Pennica *et al.* in which Dr. Goddard is a co-author of the paper. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Thus, Dr. Goddard's statement that "a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Goddard would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[1] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."[2] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner."[3] Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[4] which states, "Office personnel must accept an opinion from a qualified expert that is based upon

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[1] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[2] *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[3] *In re Alton, supra.*

[4] Part IIB, 66 Fed. Reg. 1098 (2001).

relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement from an expert in the field (the Goddard Declaration) states that "it is my considered scientific opinion that ... a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer." Therefore, barring evidence to the contrary regarding the above statement in the Goddard Declaration, this rejection is improper under both the case law and the Utility guidelines.

The Examiner also alleges The PRO1759 gene has not been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1759 nucleic acid was amplified in two types of cancer samples (lung, colon), to a minor degree (about 2.16 to 2.85 fold). No mutation or translocation of PRO1759 has been associated with any type of cancer versus normal tissue. (Page 6 of the instant Final Office Action).

It appears that the Examiner's concern is with regard to the underlying mechanism resulting in the positive gene amplification results, and not with those results themselves. However, the Examiner's concerns regarding the alleged lack of mutation or translocation of PRO1759 associated with any type of cancer versus normal tissue, in no way negate the utility of the claimed invention. The fact remains that the gene amplification results demonstrate overexpression of PRO1759 in the named tumor. One of ordinary skilled in the art does not need to know the underline mechanism of the overexpression of PRO1759, such as mutation or translocation, to practice the claimed invention. One of ordinary skill in the art, in possession of these results, would have believed it more likely than not that the PRO1759 polypeptides were useful for their asserted utility.

The Examiner also states that she "cannot find any reason to suspect, that the protein encoded by the PRO1759 gene would confer any selective advantage on a cell expressing it" and that "there is no structure/function analysis in the specification" (Page 8 of the instant Final Office Action).

Applicants respectfully traverse this rejection. Applicants submit that the request for "structure/ function data" is not a utility requirement. Neither is a showing of mechanism of action necessary for the utility requirement. Furthermore, Applicants note that selective advantage to cell survival is not the only mechanism by which genes impact cancer, and for this additional reason, this heightened requirement imposed by the Examine is improper according to the Utility standards set by the USPTO.

The Examiner further alleges that "(m)erely because aneuploidy may be an initial step in the formation of cancer does not equate with a substantial assertion of a diagnostic tool for cancer for the encoded PRO1759 protein." (Page 9 of the instant Final Office Action).

Again, Applicants need not explain the mechanism by which genes impact cancer, according to the Utility standards set by the USPTO. As discussed previously, even if the amplification observed for PRO1759 were due to aneuploidy (which Applicants do not concede to), the PRO1759 gene can at least be a marker for cancerous or pre-cancerous tissue or damaged tissue.

The Examiner further alleges that the pooled normal blood control was not a proper control. The Examiner relies on the teachings of Bieche et al. and Pitti et al. to allege that, althought they used pooled DNA controls, these authors did not use their data for diagnostic purposes, as in the instant application. (Pages 7-8 of the instant Final Office Action).

Applicants have discussed the references Pennica *et al.*, Bieche *et al.*, Pitti *et al.* and Hu *et al.*, in great detail in their Responses dated November 30, 2005 and January 25, 2007, and maintain their position regarding this matter. Applicants maintain that references Bieche *et al.* and Pitti *et al.* were presented to show the use of pooled DNA from normal, healthy donors as control was well-known and was widely utilized at the time of filing of the instant application. That the Bieche *et al.* and Pitti *et al.* used such controls for experimental purposes (and not for diagnostics, according to the Examiner) should bear no consequence to the fact that, pooled DNA controls were an acceptable control in the art at that time of filing of the instant application. Accordingly, the Examiner has not presented valid arguments or contrary evidence to show that the pooled control was not acceptable at the time of filing. Such a rejection is therefore improper.

A *prima facie* case of lack of utility has not been established

The Examiner has asserted that the gene amplification data discussed above is not sufficient to provide utility for the PRO1759 polypeptide, because allegedly there is no evidence to "to demonstrate that gene amplification correlates with polypeptide over-expression or that PRO1759 polypeptide of the instant application is supported by a specific and asserted utility or a well established utility." (Page 10 of the instant Final Office Action). The Examiner maintains that the Applicants' assertion of utility is not substantial based on the teachings of Pennica et al., Sen et al., Hu et al., Chen et al., Haynes et al., Madoz-Gurpide et al., Celis et al., Feroze-Merzoug et al., and Steiner et al. The Examiner further points to the reference by Li et al., to state that "gene amplification does not predictably or even predominantly lead to increased transcription." (Page 27 of the instant Final Office Action).

Applicants also maintain, for the reasons provided in the previously filed responses, that Pennica *et al.*, Sen *et al.*, Haynes *et a*l., Hu *et al.*, Madoz-Gurpide *et al.*, Celis *et al.*, Feroze-Merzoug *et al.*, Chen *et al.* and Hanna *et al.*, as well as, Gygi *et al.*, Futcher *et al.*, Steiner *et al.* and Li *et al.* do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. Applicants' arguments presented in the previously filed Response of January 25, 2007 and previous responses of record are hereby incorporated by reference in their entirety.

Gygi *et al.*

The Examiner points out that they are unable to locate where the Gygi et al reference discusses "accurately predicting" the precise levels of protein expression. (Page 12 of the instant Final Office Action).

Applicants submit that Gygi *et al.* clearly teach that "there was a general trend of increased protein levels resulting from increased mRNA levels." (Emphasis added. See page 1726, left column, second paragraph and Figure 5). In response to the Examiner's assertion that Gygi *et al.* teach that the correlation between mRNA and protein levels was insufficient to **predict** protein expression levels from quantitative mRNA data, Applicants maintain the law does not require the existence of a "necessary" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately predicted." According to Gygi, the

data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein.

Feroze-Merzoug *et al.*

The Examiner asserts that "Feroze-Merzoug et al. disclose that there is evidence highlighting the disparity between mRNA transcript and protein expression levels and that it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation." (Page 13 of the instant Final Office Action).

Applicants note that Feroze-Merzoug *et al.* looked specifically at androgen regulated genes, which were not necessarily associated with cancer. The expression of these genes clearly involves different biological processes than in colon and lung tumor development. Therefore, even if the teaching of Feroze-Merzoug *et al.* accurately reflects the correlation between mRNA and protein for the particular system studied, it does not apply to the cancer diagnostic assays of the present application. Feroze-Merzoug *et al.* will not suffice to establish a *prima facie* case for lack of utility because the teaching of this reference only applies to the development of hormone-refractory prostate cancer at best. It does not apply to cancer-related genes in general, let alone apply to PRO1759 which is related to colon and lung cancer. Furthermore, Feroze-Merzoug *et al.* appear to be focusing on "accurately predicting" the precise levels of protein expression, which is not required for utility as a cancer diagnostic.

Beer *et al.*

The Examiner has also asserted that she could not locate a conclusion in Beer that microarrays are a reliable measure of the expression levels of a gene. The Examiner has further asserted that, in contrast to Beer, the instant specification does not disclose any special feature, stage, or prognosis, of colon tumors. The Examiner has also asserted that "Example 143 of the instant specification utilizes the 5'nuclease assay (TaqMan) to determine gene amplification, and not a microarrya to determine mRNA expression (as in Beer)." (Page 15 of the instant Final Office Action).

Applicants submit that Beer clearly states in the Abstract that "gene-expression profiles based on microarray analysis can be used to predict patient survival in early-stage lung adenocarcinomas." This statement suggest that microarrays are a reliable measure of the expression levels of a gene related to cancer diagnosis.

Applicants fail to see why the present specification must disclose the same amount and same type of information as in Beer *et al.* Beer *et al.* was cited to show the existence of a correlation between increased mRNA levels in tumors and increased protein levels. As Beer *et al.* has already established the existence of a general correlation between increased mRNA levels in tumors and increased protein levels, Applicants do not need to disclose the same kind or amount of data as in Beer *et al.* to further prove Beer *et al.'s* conclusion. Instead, Applicants can simply rely on the conclusion of Beer *et al.* In addition, Applicants emphasize that neither the case law nor the Utility Guidelines requires that Applicants must disclose the same amount of experimental data in a patent application for the purpose of establishing a patentable utility as in an article published in a peer-reviewed journal, where extensive experimental details are typically provided. On the contrary, the Office personnel must treat as true a statement of fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. One of ordinary skill in the art would not have a legitimate basis to doubt the credibility of the results of the present application because Beer *et al.* has established the correlation between increased mRNA levels in tumors and increased protein levels.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

The Examiner repeatedly alleges in the instant Final Office Action that the specification does not establish a nexus between the DNA of the instant invention and the PRO1759 protein. Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record in Information Disclosure Statement filed on February 2, 2005) and the articles by Bea *et al.* and Godbout *et al.*

(made of record in Preliminary Amendment of August 7, 2006) collectively teach that in general, gene amplification increases mRNA expression.

Second, Applicants have submitted over a hundred references, along with the Declaration of Dr. Paul Polakis with their Preliminary Amendment filed on August 7, 2006, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Third, Applicants would like to bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9 of the Decision). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1759 polypeptide to refute Applicants' assertion of a correlation between mRNA levels and protein expression.

The Examiner asserts that the articles of record by Orntoft et al., Hyman et al., Pollack et al., Bea et al. and Godbout et al. do not support a general mRNA/protein correlation, and that Hyman et al. and Pollack et al. did not look at polypeptide levels. (Pages 20-23 of the instant Final Office Action).

Applicants respectfully submit that the Hyman *et al.,* and Pollack *et al.* references, as stated in Applicants' previous Responses, teach that in general, gene amplification increases mRNA expression. Applicants further submit that Dr. Polakis' Declarations and Dr. Scott's Declaration were presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Thus, taken together, all of the submitted evidence supports Applicants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Orntoft *et al.*

The Examiner maintains that the Orntoft et al., reference is not persuasive because "the methodology used in the Orntoft reference is different from that of Applicant. (Page 21 of the instant Final Office Action).

The Orntoft reference was submitted by the Applicants to show that there was a gene dosage effect and teaches that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts." (See column 1, Abstract). Based on this reference and on several other references, Applicants have submitted that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method.

The Examiner further criticizes Orntoft et al. on the basis that Orntoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There allegedly was no comparison between genes in cancerous versus non-cancerous tissue. (Pages 21-22 of the instant Final Office Action).

Applicants note that Orntoft *et al.* state that it was a strength of the investigation that they were able to compare invasive tumors to benign tumors rather than to normal urothelium, as the tumors studied were biologically very close and probably represent successive steps in the progression of bladder cancer. (Page 44). Accordingly, the identification of the correlation by Orntoft *et al.* of a correlation between gene amplification and mRNA overexpression is more meaningful.

The Examiner criticizes the specification on the basis that the specification allegedly discloses low levels of amplification of DNA. (Page 27 of the instant Final Office Action). Applicants note that Orntoft *et al.* states that chromosomal areas with more than a 2-fold gain in DNA showed a corresponding increase in mRNA transcripts. (Abstract) Applicants note that they have shown a more than 2-fold amplification of PRO1759 DNA in Example 143.

Hyman *et al.*

The Examiner further asserts that the Hyman reference "found 44% (less than half) of highly amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate." (Page 22 of the instant Final Office Action).

Applicants submit that the 10.5% figure is not relevant to the issue at hand. One of skill in the art would understand that there can be more than one cause of overexpression. The issue

is not whether overexpression is always, or even typically caused by gene amplification, but rather, whether gene amplification typically leads to overexpression.

The Examiner's assertion is not consistent with the interpretation Hyman *et al.* themselves place on their data, stating that, "The results illustrate **a considerable influence of copy number on gene expression patterns**." (Page 6242. col. 1; Emphasis added). In the more detailed discussion of their results, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (***i.e.*, belonged to the global upper 7% of expression ratios**) compared with only 6% for genes with normal copy number." (See page 6242, col. 1; Emphasis added). These details make it clear that Hyman *et al.* set a highly restrictive standard for considering a gene to be overexpressed; yet almost half of all highly amplified transcripts met even this highly restrictive standard. Therefore, the analysis performed by Hyman *et al.* clearly shows that it is "more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

Pollack *et al.*

The Examiner further alleges that "Pollack et al, using CGH technology, concentrate on large chromosome regions showing high amplification (p. 12965). However, Pollack et al. did not investigate or show a relationship with amplification and polypeptide expression. (Page 23 of the instant Final Office Action).

As previously submitted, Pollack *et al.* profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also

on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted over one hundred references, along with the Declaration of Dr. Paul Polakis with their Preliminary Amendment filed on August 7, 2006, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Meric *et al*

With respect to Applicants' arguments on Meric et al., the Examiner asserts that Meric teaches that the gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. (Page 24 of the instant Final Office Action).

Applicants emphasize that it is not a legal requirement to establish an absolute correlation between an increase in the mRNA level and protein expression levels that would correlate to the disease state nor is it imperative to find evidence that protein levels can be accurately predicted. Therefore, the Examiner has misinterpreted the teaching of Meric and applied improperly high legal standard.

Applicants respectfully submit that Meric simply summarizes the translation regulation of cancer cells. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled with cell cycle progression and cell growth. Meric further discusses that alteration in translation control occur in cancer. For example, variant mRNA sequences can alter the translational efficiency of individual mRNA molecule. (see Abstract). Meric further teaches that the changes of the translational efficiency of a mRNA transcript depend on the mutation of a specific mRNA sequence. (Page 973, column 2 to page 974, column 1). Meric never suggest that the translation of a cancer gene is suppressed in cancer in general, and therefore, an increased mRNA levels will not yield an increased protein levels. To the contrary, Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to its normal counterpart. For instance, in patient with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation. (Page 974, column 1). Therefore, the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the mRNA

level. As absolute accurate prediction of the protein level based on the mRNA level should not be required, the Examiner has failed to establish a *prima facie* showing of lack of utility in this instance.

Celis *et al.*

According to the Examiner, Celis et al. also teaches that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed, but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules." (Page 17 of the instant Final Office Action).

Applicants submit that significant correlations between gene and protein expression are most likely to be observed for genes associated with cancer, since as Celis *et al.* note, "transformation resulted in the abnormal expression of normal genes, rather than in the expression of new ones." (Page 11, col. 1). Accordingly, alterations in gene amplification or expression are more likely to be associated with altered protein expression in the case of cancer than in other cases where DNA microarrays are used, because, as explained by Celis *et al.*, the alterations in expression levels of certain normal proteins are part of the process that leads to cancer.

In their discussion of DNA microarrays and proteomics applied to the same samples, Celis *et al.* cite Ornfoft *et al.*, and note that "in most cases there was a good correlation between transcript and protein levels." Celis *et al.* further explain that those few cases which showed apparent discrepancies may have been due to other causes, such as post-transcriptional processing or degradation of the protein, or the choice of methods used to assess protein expression levels. Celis *et al.* also note that the observation that there is often more change in mRNAs as compared to the proteins may be due to the fact that current technologies detect mainly high abundance proteins, while most of the changes affecting protein levels may involve low abundance proteins. Thus, the correlation between mRNA and protein levels may be even higher than typically observed, given these factors.

Previously cited supporting references

The Examiner asserts that the newly cited references (except Bea et al and Godbout et al.) do not measure gene amplification. The Examiner further alleges that the mere existence of 149 references that do not provide consistent teaching to support Applicants' case is evidence of the unpredictability in the art. (Pages 25-26 of the instant Final Office Action).

Applicants have acknowledged that the new references focus on the correlation between mRNA expression and protein expression levels, and for the most part do not examine gene amplification. However, those few references that actually looked at gene amplification **did** find a correlation between gene amplification and increased mRNA and protein expression levels. In addition, Applicants note that regardless of how mRNA and protein are measured, the fact that the submitted references measure mRNA with many different assays confirms that such a correlation is observed when varied experimental methods are used.

Applicants further note that the submitted references, which represent the experiments conducted by a large number of different study groups, exactly demonstrate a trend of correlation found across proteins in general, because this trend is confirmed by an overwhelming number of experiments by different researchers, using diverse experimental designs, testing various types of tissues at numerous biological conditions. Although only a single gene or a small group of genes was tested by an individual study group, the cumulative evidence by over one hundred study groups certainly establishes that it is well-accepted in the art that a general mRNA/protein correlation exists.

Applicants respectfully submit that it is not a legal requirement to establish a absolute predictability that the mRNA level of a gene correlates with the corresponding protein level of the gene because, as discussed in the previously filed Responses, the correct utility standard is not "absolute certainty."

In response to Applicant's arguments that Bea et al. clearly supports Applicants' assertion that gene amplification is correlated with both increased mRNA and protein expression, the Examiner further asserts that Bea et al. performed a number of validation test before reaching their conclusion, while the instant specification does not complement PRO1759 gene expression data with any other mRNA or protein studies. The Examiner further asserts that

Orntoft et al., Hyman et al. and Pollack et al. utilize different methods from the instant specification and Godbout et al. (Page 26 of the instant Final Office Action).

The Examiner fails to provide any reason why the present specification must disclose the same amount and same type of information as in Bea *et al.* Bea *et al.* and Godbout *et al.* were cited to show the reliability of the gene amplification typically leads to mRNA and protein overexpression.

As Bea *et al.* and Godbout *et al.* have already demonstrated the relationship between gene amplification, mRNA expression and protein expression, Applicants do not need to disclose the same kind or amount of data as in these references to further prove their conclusion. Instead, Applicants can simply rely on the conclusion of Bea *et al.* and Godbout *et al.* In addition, Applicants emphasize that neither the case law nor the Utility Guidelines requires that Applicants must disclose the same amount of experimental data in a patent application for the purpose of establishing a patentable utility as in an article published in a peer-reviewed journal, where extensive experimental details are typically provided. On the contrary, as discussed in the previously filed Preliminary Amendment, the Office personnel must treat as true a statement of fact made by an Applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. One of ordinary skill in the art would not have a legitimate basis to doubt the credibility of the results of the present gene amplification assay because Beer *et al.* and Golub *et al.* have established the relationship between gene amplification, mRNA expression and protein expression.

Applicants further point out that Bea *et al* never suggest that gene amplification data must be confirmed by additional mRNA or protein expression studies. Bea *et al.* simply further tested the protein or mRNA expression of the identified genes in the gene amplification analysis with other techniques available in the art, such as Southern blot, RT-PCR and Western blot. It turned out that the test results obtained from these techniques were consistent with the observation in the gene amplification analysis, confirming that gene amplification analysis is a reliable tool for studying gene expression regulation. This reliability having been confirmed by, among others,

Bea *et al.*, it is not necessary for every subsequent gene amplification analysis to repeat the same confirmatory experiments.

The Examiner asserts that "the levels of amplification shown for PRO1759 were not of a high enough level to be predictive of protein increases, for reasons amply of record." (Page 27 of the instant Final Office Action).

Applicants respectfully point out that the record does not show any evidence provided by the PTO to indicate what levels of gene amplification are "high enough" to be predictive of protein increases. As discussed above and in previous responses of record, the levels of amplification for PRO1759 were **not** "low" but significant, and ranged from 2.16-fold to 2.85-fold, in three different lung and colon tumors. Applicants also respectfully point out that the Examiner appears to be confusing DNA levels with protein levels. While the proteins studied by Orntoft *et al.* were abundant, this has nothing to do with the DNA levels observed to correlate with increased gene and protein expression. As discussed previously, Orntoft *et al.* found that the level of gene amplification associated with expression changes was only around two-fold, even less than the 2.16-fold to 2.85-fold amplification observed for PRO1759. Even with these relatively low levels of gene amplification, Orntoft *et al.* found that "**[i]n most cases,** chromosomal gains detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%)" (page 40, col. 2; Emphasis added). The level of correlation between DNA copy number and increased mRNA levels observed by Orntoft *et al.*, from **77-80%**, clearly meets the standard of more likely than not. Orntoft *et al.* also found a "highly significant" correlation between mRNA and protein levels, with the two data sets studied having correlations of 39/40 (**98%**) and 19/26 (**73%**) (pages 42-43). Therefore, Applicants submit that the art of record clearly demonstrates that the degree of amplification observed for PRO1759 in lung and colon tumors is well within the range known to be correlated with increased gene and protein expression.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1759 polypeptides, for example, in detecting over-expression or absence of expression of PRO1759. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based

on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides. Hence, these data clearly support a role of PRO1759 as a lung and colon tumor marker.

Therefore, Applicants request that the Examiner reconsider this rejection and maintain that they have demonstrated utility for the PRO1759 polypeptide as diagnostic markers for human lung and colon tumors. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph, utility rejections should be withdrawn.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Scope of Enablement)

Claims 28-32 and 39-40 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for the claimed variant polypeptides. (Page 29 of the instant Final Office Action).

Applicants respectfully maintain the position that that Claims 28-32 and 39-40 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in Applicants' Responses filed on February 2, 2005, November 30, 2005 and in the Preliminary Amendments filed on July 21, 2005 and August 7, 2006.

III. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-32 and 39-40 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description. (Page 30 of the instant Final Office Action).

Currently pending Claims 28-32 and 39-40 recite the functional limitation that the nucleic acid encoding the polypeptide is amplified in lung and colon tumors. Accordingly, coupled with the general knowledge available in the art at the time of the invention, Applicants submit that the specification provides ample written support for the claimed polypeptides in Example 143, where methods of detecting and quantifying amplification in several tumors and/or cell lines are described. Thus, based on the high percentage of sequence identity and the described method of detecting and quantifying amplification in tumors, one skilled in the art would have known at the time of the invention that the Applicants had possession of the claimed polypeptides.

For the above reasons, and for the reasons discussed in the previous Responses filed on February 2, 2005, November 30, 2005, and in the Preliminary Amendments filed on

July 21, 2005 and August 7, 2006. Applicants respectfully request reconsideration and reversal of the written description rejection of Claims 28-32 and 39-40 under 35 U.S.C. §112, first paragraph.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C38**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 13, 2007

By:_____
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